Towards Hybrid Therapeutic Strategies in Intellectual Disabilities

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Abstract

I present and discuss what I see as a decisive convergence between future (no longer science fiction) genetic therapies in human beings with intellectual disabilities and standard (so to speak) neurobehavioral interventions. This crossing will lead to a radical modification in the life prospect of people with intellectual disability from genetic origin. Changing their previous biological status into a condition that can be substantially improved with refined knowledge and technical tools. Such a change, in the longer turn, could impact on ordinary people's conceptions and henceforth attitudes regarding the persons with intellectual disabilities. It might gradually lead to a reversal of the present trend of pregnancy termination following a confirmed diagnosis of genetic syndrome, significantly favoring instead a 'let live and help' moral and social attitude.
Keywords: Hybrid interventions; language intervention, early intervention

Introduction

Early intervention (EI) may be defined as the set of knowledge-based clinical activities with the intellectually disabled (ID) child and her/his family between birth and approximately six years that intends to eliminate, prevent, or compensate for the developmental delays and deficits of the condition. The strategy is to take advantage of the earlier ages to activate, promote, and optimize neurobehavioral structures and processes which would remain underdeveloped due to adverse neurogenetic effects on the ontogenesis.

There are several justifications for carrying out systematic intervention. In the case of a congenital ID condition, assuming early diagnosis, it is advisable to initiate intervention in the weeks following birth in order to reduce as much as possible the delays in the socio-personal, physical, and cognitive aspects of development. Human ontogenesis is highly cumulative. Earlier acquisitions serve as a basis for further developments. The sooner the basic structures are in place, the better the prognosis for additional progress and the higher the probability, assuming continued training, that advanced levels of development as allowed by the condition will be reached. A second reason is that brain plasticity is larger during the first years of life, and this also applies to children with ID therefore supplying a more fertile receptive ground for intervention. The two reasons above suggest that EI is likely to be more cost-effective than any intervention carried on later in life which is not to say that the latter is devoid of value or that intervention with children with ID should be discontinued after six years of age. Guralnick (1997, 2005) has reviewed current knowledge underlying a number of development-enhancing dimensions, concluding that decades of both small- and larger-scale studies indicate that an affirmative answer is warranted to the question whether we are capable of altering individual development through EI programmes. Guralnick (2005) reckons that comprehensive EI programmes have proved able to prevent much of the decline in cognitive development for children with Down syndrome (DS) occurring during the first years. Although demonstrating longer-term effects present difficult methodological challenges, long-term outcomes years later have been documented as well for several developmental pathologies including DS. Guralnick (2005) also suggests directions for future research and practice, among them specifying better subgroups of children and families in research and evaluation studies (etiological and genetic specificity), identifying better the specific components of intervention responsible for producing sought-after effects, calibrating the intensity of intervention, and assessing better patterns of interaction between subgroups based on child's and family characteristics and programme components.

But why, it could be asked, should one devoid so much attention to EI and future prospects at a time where, due to the conjunction of fetal diagnosis and abortive practices, the occurrence of babies with DS (and other genetic causes of ID if not today probably tomorrow) is decreasing in a number of Western countries? Should we not better concentrate our energies on caring for adults with ID who,

given the marked increase in their life expectancy, will be more prevalent in coming years than ever in the past?

We should certainly pay much attention to this last issue and launch more research and clinical works intending to clarify several of the most urgent problems arising as a consequence of a longer living in persons with ID, such as a propensity towards earlier physiological aging and a higher susceptibility to Alzheimer disease in persons with DS. In my opinion, however, the case for EI is far from being closed for reasons that will become apparent in the rest of the paper.

Let's take a look at the present-day attempts with animals at genetic therapy in the case of experimentally induced pathological conditions akin to some genetic conditions of ID in humans. Major progresses in molecular genetics over the last decades have made possible to chart a number of mammalian genotypes including the human one composed of a little less than 33.000 genes distributed over 23 pairs of chromosomes. Although the particular locations of these genes are known their exact function in cell functioning has not been specified yet except for a few hundred ones. However, the available knowledge is already sufficient to support the definition of animal analogs to some conditions leading to ID such as fragile X – FXS - (etiologically linked to a mutation of the gene FMR-1 or FMR-2 on chromosome X) and Down syndrome (trisomy 21). For example, trisomy 21 in humans is at least partially mimicked (genotypically and phenotypically) in mice by experimentally induced trisomy 16. Recent work suggests that it is possible to ameliorate, at least partially, FMR-1 knockout (KO) mice, an animal model of fragile-X, at both cellular and behavioral levels in inhibiting the catalytic activity of p21-activated kinase (PAK), a kinase known to play a critical role in actin polymerization and dendritic spine morphogenesis (Hayashi et al., 2007). Greater spine density and elongated spines in the cortex, morphological synaptic abnormalities commonly observed in FXS, are at least partially restored by postnatal expression of a dominant negative PAK transgene in the forebrain. Likewise, the deficit in cortical long-term potentiation observed in FMR-1 KO mice is fully restored by the PAK transgene. Several behavioral abnormalities associated with FMR-1 KO mice, including those in locomotor activity, stereotypy, and anxiety are also partially ameliorated or eliminated by the PAK transgene. Particularly interesting is the fact that in vivo data in mice suggest that PAK inhibition is still possible after the appearance of the FXS symptoms. FMR-1 KO mice exhibit abnormalities as early as the first postnatal week. In human patients with FXS developmental delay appears as early as 9-12 months of age and diagnosis usually shortly follows. Current data suggest that PAK inhibition could still be an effective therapy for FSX infants even during the first year of life ex utero.

Other gene-based strategies exist targeting either gene products or downward pathways (Delabar, 2007). Prolongating the action of the gene material (deoxyribonucleic acid – DNA) outside of the cell nucleus is RNA messenger (ribonucleic acid). Any excess in DNA products (for example, in trisomies) is thought to determine an increase of the corresponding messenger RNA. The use of a small class of small RNAs, the interfering RNAs or siRNAs, is one of the strategies allowing to decrease, first, the amount of the targeted RNA and, second, the amount of encoded proteins. siRNA molecules can selectively silence any gene in the genome. Applied to a mouse model of amyotrophic lateral sclerosis, a mutated form of superoxyde dismutase 1 (SOD 1) has been experimentally targeted, reducing its expression, improving survival of vulnerable motor neurons, and mediating an improved motor performance in these animals (Delabar, 2007).

A second strategy is to target the protein product of the candidate gene. For example, antibodies can be used to decrease the amount of amyloid beta peptides derived from the amyloid precursor protein. In mice, by direct hippocampal perfusion, researchers were able to restore hippocampal acetylcholine release and reduced impaired habituation learning (Pritchard & Kola, 2007).. This work offers hope for a therapeutic potential of targeting amyloid beta peptide overproduction in Alzheimer patients or in DS patients with Alzheimer disease incipiens.

A third possibility is to use chemical compounds that serve to modify the activity of the target protein or the targeted physiological pathway. For example, minibrain kinase/dual-specificity tyrosine

phosphorylation-regulated kinase (Mnb/Dyrk 1 A) is a kinase encoded by a gene located within the DS chromosomal critical region DSCR-1 (Korenberg et al., 1997). Its expression is elevated in individuals with DS and it is thought to be involved in the control of neurogenesis. Research in vitro shows that this type of kinase is inhibited by a natural molecule that is the main component of the polyphenols in green tea. Delabar (2007) has reported in vivo successful attempts to partially correct the alterations in the brain morphogenesis of transgenic mice using a diet rich in polyphenols given to pregnant mothers and continued postnatally until the magnetic resonance imaging (MRI) performed between 2 and 4 months of age in the offsprings. These results suggest that it is possible to improve a brain phenotype by the use of some particular molecules which do not affect the rest of the organism.

Two general hypotheses have been proposed to explain the DS phenotype: (1) the amplified developmental instability hypothesis suggesting that DS is the result of a disturbance of chromosome balance due to the additional chromosome material; and (2) the gene dosage hypothesis proposing that the DS phenotype stems directly from the effects of the overexpression of specific gene products on a portion of chromosome 21 (HSA21) and/or indirectly through the interaction of these genes with the whole genome, transcriptome (transcription events from DNA to RNA), or proteome (protein synthesis following the instructions listed in the genes). Evidence from murine models points to specific genes affecting phenotypes rather than non-specific effects of the amount of extra-genetic material (Pritchard & Kola, 1999). It appears, however, that the comprehensive DS phenotype cannot be accounted for on the basis of gene dosage effects alone. In fetuses or adults with DS, a number of genes across the genome are expressed at either higher or lower transcriptional levels than normal (Jenkins & Velinov, 2001). In this respect, it is interesting to note that some murine approaches have introduced large foreign DNA pieces with homologies with HSA21 in the animals' genome. Such approaches overcome some of the limitations of single-gene transgenics as the models involve the utilization of overlapping or contiguous parts that cover a significant part of the chromosome.

Targeting specific genes or fragments of the genome in animal models is now possible. However, the corrective interventions may create negative side-effects that have to be controlled or suppressed. Rescuing strategies with a larger scope are also being considered. For example, Pritchard and Kola (2007) have studied the effects of a transcription factor known as Ets2. This factor regulates the expression of numerous genes involved in cell cycles, cell survival, and tissue remodeling. In mice, over-expression of Ets2 produced some of the skeletal abnormalities characteristic of DS, as well as a smaller thymus similar to that seen in DS, and increased neuronal apoptosis. It would appear that Ets2 up-regulate pro-apoptotic genes and down-regulate anti-apoptotic genes analog to corresponding HSA21 genes in mice. This trend of research supplies a beginning picture of the cellular function of transcription factors regulating the cellular effects of genes. They open the door to new drug therapies that will act specifically in the pathways disrupted by the chromosome imbalances. New perspectives in cell therapy (Hornyak, 2008) showing that it is possible to reprogramming normal adult human cells into the perfect equivalent of pluripotent stem cells (i.e., cells which like embryonic cells can develop into any type of tissue), thus bypassing the need to use human embryonic cells, also offers hope to allow replacing some defectuous human tissue with normal ones while avoiding the threat of immune rejection if cells derived from an embryo are transplanted into a person.

The genetic conditions etiologically linked to a single gene mutation (such as FXS or Rett syndrome) will likely be the first to witness rescuing altered brain phenotypes within the span of a few years. Syndromes characterized by missing genetic material (such as Williams syndrome, Cat-cry syndrome, or Turner syndrome 45 XO) will be harder to come by. Progresses have been made in recent years in inserting new or modified genes into a person's cells to treat or prevent disease (e.g., Hemophilia B and X-linked immunodeficiency; Sepa, 2000). Already in advanced clinical trials in the USA, are the treatments of hereditary disorders such as cystic fibrosis by delivering functional copies of missing genes to cells that need them. Heart treatment of the kind is also under consideration. Immune cells are helping to hunt down cancer cells and make the system resistant to infection. Scientists currently use modified viruses (e.g., retroviruses, adenoviruses) as vectors to deliver gene therapy. Viruses are good at delivering genetic material to cells because this is what they do naturally.

The strategy is to strip viruses of their own genetic material and replace it with therapeutic genes which they will deliver to the cell. Different viruses do different things. Some attack the liver, other nerves. Some insert their DNA into the host genome. So, genetic therapists can choose those viruses that best suit their purpose and further engineer them if desirable. There is a catch, however. Our immune system evolved to reject viruses. So even if a virus reaches its target, one must ensure that the receptive body does not attacked the "reengineered cells" because they might be identified by the immune system as "infected" cells. There is a number of particular strategies that scientist are developing to annihilate this sort of complication (e.g., lowering therapy doses, pre-treating patients with immunosuppressive drugs, making viral vectors so immune that the immune system will not detect them). Some approaches are developing "naked"(vectorless) DNA and genes packaged in other and less intrusive ways. In utero gene transfer can be achieved. Various ex vivo and in vivo successful techniques have been reported (Ye et al., 2001). Ex vivo techniques require the removal of the target cells from the fetus. The cells are "infected" with the virus carrying the foreign gene and re-infused into the fetus. In the in vivo technique, the vector is directly administered to the fetus and infection/transduction occurs within the fetus in utero. Gene transfer introduces certain risks to both mother and fetus, but more to the fetus (e.g., potential toxicity of gene transfer, immune reactions, damage impacted on fetal development, possible tumor formation) which need to be carefully checked. In utero gene therapy has generated controversy (Caplan & Wilson, 2000). Some scientists are concerned that genetic technology could be moving too far ahead of existing knowledge of the natural history of diseases (Billings, 1999). Others insist that in utero therapy is ethical based on providing an alternative to abortion for a fetus with a severe genetic defect detected prenatally (Moulton, 1999).

Aneuploidies such as trisomy 21 (DS) will also be harder to come by but for another reason: the large number of genes the protein products of which have to be corrected. The DNA sequencing of HSA21 has been completed (Hattori et al., 2000). Chromosome 21 is the second smallest human autosome extending for a total of 33, 8 Mb. It is predicted to contain from 261 to 364 protein-coding genes involved in 87 different biological processes. The exact function of many of these genes remains unknown, as does their individual contribution, if any, to the DS phenotype. However, it is known that numerous proteins encoded by genes located on HSA21 can affect the structure and/or the function of the brain. A short list is already available containing 25 entities (Wisniewsky et al., 2006). Based on the analysis of human individuals with partial segmental trisomy 21, it has been possible to identify a DS critical region (DSCR) located in the q part of chromosome 21 and encompassing a 1.2 Mb region around D21S55 (Peterson et al., 1994). This is the part of HSA21 where genetic loci presumably display genes with major effects regarding the DS phenotype (e.g., somatic features, developmental delays, cognitive disability). There is no a priori way to determine the exact number of genes involved in the genesis of a complex phenotype. Assuming linear distribution of the genes along HSA21, one could speculate that the DSCR contains something like a dozen genes. One should not forget, however that interactions between DSCR genes and other genes located on chromosome 21 as well as perhaps on other chromosomes also contribute to the phenotype. Additionally, not all genes on HSA21 may be are dosage-sensitive, i.e., potentially harmful when triplicated (which increases expression by 50% at the RNA and protein levels). Even so, the number of candidate genes for genetic intervention provides for unique complexities in the case of DS. Partial human trisomies 21 will be easier to compare with the mice models consisting in corresponding partial trisomies. The mouse orthologs of the human genes located on HSA21 are on chromosomes 10, 16, and 17. Mice trisomic for fragments of chromosome 16 corresponding to 132 genes on HSA21, in one case, and to 85 genes, in another case, are available (Davisson et al., 1990; Sago et al., 1998). The transgenic mice present a series of features of DS: cranial abnormalities, developmental delay, learning difficulties, neuronal reduction in some parts of the brain, reduction in cerebellar volume (Baxter et al., 2000).

Rescuing the complete phenotype in DS appears today a formidable task. However, given that strategies targeting specific genes are already yielding promising results, a pragmatic approach consisting of inhibiting particular gene products and cautiously avoiding possible negative effects, is something that could soon be on the clinical agenda. The immediate objective would not be to cure DS as such, but gradually improve the phenotype. "It is probably not essential that we know all the

genes on chromosome 21 before rational therapies can be considered" (Epstein, 1999, p.221). Early diagnosis will then possibly become an event with positive consequences for the fetus and the infant and no longer be a death sentence. Phenotypic plasticity is greatest in early years (which does not mean that it is restricted to these periods; the brain remains a plastic and highly malleable organ throughout life; Bailey et al., 2001), the sooner phenotypic development can be rescued, the better for the rest of the ontogenesis given its cumulative character.

In so doing, the ground will be better prepared for enhancing dramatically, it can be hypothesized, the effects of early neurobehavioral intervention. With all the potential inherent in the genetics advances, it is easy to lose sight of some caveats. As genomic science moves forward, we will increasingly be in a better position to determine the precise effects of neurobehavioral interventions on gene functioning and expression (Reiss & Niederhiser, 2000). Genetic factors alone account for only a fraction of variance in human behavior. To account for the remaining variance, one must move towards analyses of functional interactions between biology, environment, and behavior (Rutter, 2002).

Probably the greatest potential of the neurosciences resides in its integration with expanding knowledge of genomics. We should be heading towards hybrid intervention approaches (Warren, 2002), i.e., approaches in which neuroscientists will focus more on how genes express themselves in terms of brain functions and behaviors. This will require an unprecedented degree of interdisciplinary understanding and collaboration.

Experimental studies on early environmental enrichment in animals demonstrate positive effects on neurogenesis (e.g., an increase in dendritic arborization and in length of dendrites in cortical neurons) correlated with enhanced performances in learning, memory, and visual acuity in rats and mice, suggesting that neural circuits are modified in order to optimize multiple levels of information processing and storage (Fernandez-Teruel et al., 1997; Prusky et al., 2000). The same appears to hold for Ts65Dn mice, the partial trisomic model generated by Sago et al. (1998), and referred to above, whereby it was shown that exposure to complex environments has the capacity to modulate behavior just like in euploid mice (although the exact neural mechanisms that are modified are still under discussion and there may be differences to be explored further according to the sex of the animals; Martinez-Cué et al., 2002; Dierssen et al., 2004).

The knowledge currently generated and future developments in the life sciences will enhance tremendously the possibilities of better outcomes for individuals with intellectual and developmental disabilities.

Future changes in the prognosis of DS, for example, could have an impact on the way people conceptualize the condition. If it can be improved markedly through the application of the strategies envisaged above and/or some new breakthroughs in future years, the social pressures will no longer act in favor of terminating a pregnancy because the fetus has been diagnosed with a severe form of developmental disability, but in the opposite sense, that of keeping alive a baby whose developmental prognosis is much better assuming efficient hybrid intervention right from the start, because it would be a terrible shame on all grounds to deprive a human being so close to normality of the right to live. Tomorrow our already enhanced ability to scan an individual's DNA at birth will be applied before birth with the same objective of launching therapeutic action as early as possible.

The frequency of aneuploidies following human conception is high. Trisomy 21 is not the most frequent form of aneuploidy recognized during gestation. There are other forms that are much more frequent. It is estimated that roughly 15% of known conceptions are spontaneously aborted and that half of these are genetically abnormal. If one goes earlier in gestation and look at conceptions that last no more than a couple of weeks, the frequency of aneuploidies is even higher. No predisposing factor has been identified except maternal age and perhaps the influence of the apolipoprotein E genotype. Epstein (1999) speculates that there seems to be something inherent in human reproduction that causes or allows the rate of meiotic non-disjunction to remain at a high level. Evolution should

have worked the other way around, i.e. reducing this rate as it decreases the ability of the species to reproduce. It could be that the relative fragility of human meiosis is related to some vital cell process of which we know nothing, as it is unlikely that evolution would have kept a failing reproductive mechanism for no biological reason.

Since people will continue to be conceived with trisomy 21 (or other aneuploidies) no matter what we do, we would like to be able to prevent the central nervous system deficits from occurring. The techniques for efficient neurobehavioral intervention are with us today and they have begun to be widely used in developed countries. There is little doubt that they can be improved and specified further. Early neurobehavioral intervention is not and will not be in competition with genetic therapeutic approaches. That is why while waiting some more time yet for the human genetic approach to materialize, scientists must continue improving the EI approach on the ground that the efforts and energies spent are well directed not only for the present but also for future times.

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